Chapter 3

Advanced Radiation Treatment Planning of Prostate Cancer

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Additional information is available at the end of the chapter

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Abstract

External beam radiotherapy has been playing a major role in the treatment of prostate cancer with excellent tumor control. Also, localization of prostate is a big challenge for excellent treatment, so we focus on actual IGRT techniques (ultrasound, EMF, etc.) for intrafraction and interfraction motion detection. We investigate several studies related with dose distribution of treatment planning techniques. Several studies have demonstrated the superiority of volumetric modulated arc therapy (VMAT) plans in prostate cancer. We also investigate hypofractionation and stereotactic radiation outcome instead of conventional fractionation for prostate cancer. We mention about prostate cancer's treatment in future by using MR-based linac online adaptive radiotherapy.

Keywords: VMAT, IMRT, IGRT, prostate cancer

1. Introduction

Prostate cancer is one of the most common cancers in the world, and the population of patients with intermediate-to-high-risk localized prostate cancer occupies a large proportion. Most prostate cancers are diagnosed at an early stage, allowing for the high rate of success with localized treatment. Between 30 and 45% of men receive radiation as their primary treatment for prostate cancer depending on their age [1, 2]. External beam radiotherapy (EBRT) and brachytherapy can be used for the treatment of prostate cancer. The differences and roles of these two techniques rely on the physical properties of the radiation and its delivery method. The goal of radiotherapy treatment is to deliver a powerful dose of radiation that will kill the cancer but to do it as precisely as possible so that we cause minimal damage to the healthy tissue such as the urethra, rectum, bladder, and bowel around it. External beam radiotherapy is used as a curative

treatment in men with localized prostate cancer (stage T1 or T2) or with locally advanced disease. External beam radiotherapy can also be very helpful to men with advanced prostate cancer. It can ease pain in the bones and reduce the likelihood of having a fracture. Three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT) techniques are all applied for this purpose.

2. Treatment planning and image-guided radiotherapy (IGRT) methods

The prostate and seminal vesicles are located between the rectum and the bladder. The position of the prostate is affected by physiologic changes in the bladder and rectum volume. These variations in position and shape can be left unchanged and compensated with margins or reduced by image guidance resulting in smaller irradiated volumes. Smaller margins reduce the dose to the organs at risk; therefore, effort has been directed at reducing uncertainties with the use of image guidance. Radiation oncology has seen a rapid increase in the use of image-guided radiotherapy (IGRT) technology for prostate cancer patients. Conformal high-dose radiotherapy delivered with conventional fractionation results in a significant biochemical control with acceptable toxicities and currently represents the standard therapy when radiotherapy is chosen as primary treatment.

2.1. Three-dimensional conformal radiotherapy (3DCRT) technique

3DCRT uses computed tomography (CT) scanning to plot exact anatomy and to come up with the optimal radiation dosages. 3DCRT can accurately use a patient's unique anatomy to deliver radiation exactly where the patient needs it, while avoiding the bladder, rectum, urethra, and bowel. Conventional 3DCRT treatment planning is manually optimized. This means that the treatment planner chooses all beam parameters, such as the number of beams, beam directions, multileaf collimators (MLCs), shapes, weights, etc., and the computer calculates the resulting dose distribution. 3DCRT in prostate cancer patients is a highly sophisticated and time-consuming method of dose delivery.

2.2. Intensity-modulated radiotherapy (IMRT) technique

In the treatment of prostate cancer, IMRT was introduced in the early 1990s at a number of centers. After advance IGRT methods were implemented to clinic, IMRT technique started to be more popular. IMRT, like 3DCRT, uses high-tech computer software and relies on more than 100 digital CT scans to build a three-dimensional picture of the prostate tumor and organs at risks (OARs), but it can supply even more conformal dose distribution than 3DCRT. We can modulate the intensity of each beam during treatment with a MLC. In the case of IMRT, dose distribution is inversely determined, meaning that the treatment planner has to decide before the dose distribution he wants and the computer then calculates a group of beam intensities that will be produced, as nearly as possible to the desired dose distribution. We can maximize the dose of radiation to the tumor volume and minimize the dose that affects the healthy tissue

nearby. With the largest experience being detailed at the Memorial Sloan Kettering Cancer Center. Zelefsky et al. [3] reported on the treatment of 1571 patients with IMRT at doses as high as 81 Gy, with rates of gastrointestinal (GI) and genitourinary (GU) toxicity less than those reported from their institution for 3DCRT at similar or lower doses. Likewise, Kupelian et al. [4] reported results on a large study involving 770 patients treated at the Cleveland Clinic with intensity-modulated techniques at biologically effective doses comparable with those at the Memorial Sloan Kettering Cancer Center and with similar low rates of GI and GU toxicity. This means less collateral damage to noncancerous tissue that's just minding its own business right next to the tumor in the bladder and rectum and fewer side effects.

2.3. Volumetric modulated arc therapy (VMAT) technique

Volumetric modulated arc therapy (VMAT) has attracted increasing attention because of its greatly improved delivery efficiency over fixed-field IMRT. Unlike IMRT, which typically includes less than 10 fixed-field beam angles, VMAT includes a large number of beam directions from an arc trajectory and delivers doses dynamically during rotation of the gantry.

VMAT is a novel radiation technique, which can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues compared with conventional radiotherapy techniques. VMAT also has the potential to offer additional advantages, such as reduced treatment delivery time compared with conventional static-field IMRT. The clinical worldwide use of VMAT is increasing significantly [5].

3DCRT was incapable of covering a modern radiotherapy volume for the radical treatment of prostate cancer. These volumes can be treated via conventional IMRT and VMAT. VMAT was

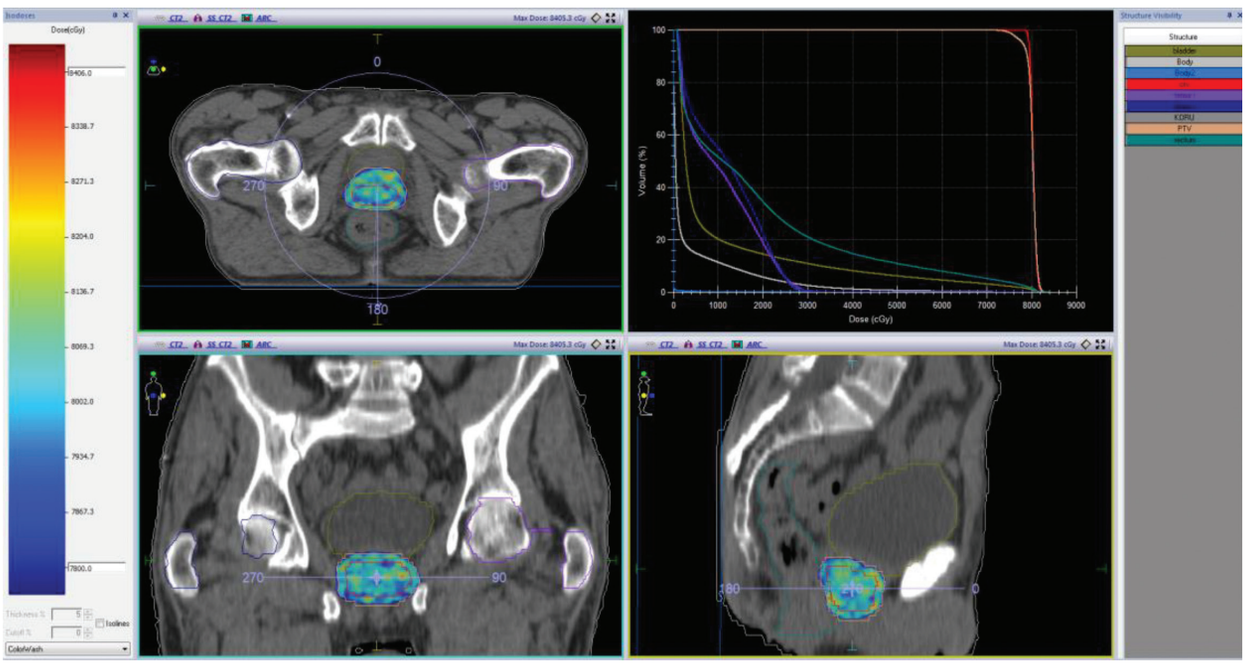

Figure 1. Dose distribution of prostate cancer treatment planning by using VMAT technique.

significantly more efficient than IMRT. VMAT technologies are a superior way of delivering IMRT treatments [6]. VMAT treatment plan is shown in **Figure 1**.

VMAT has slightly better CI, while the volume of low doses was higher. VMAT had lower MUs than IMRT. VMAT can shorten room times and improve patient throughput over seven-field DMLC IMRT.

2.4. Image-guided radiotherapy (IGRT) methods

Radiation oncology has seen a rapid increase in the use of image-guided radiotherapy (IGRT) technology for prostate cancer patients over the past decade. Prostate can move around in there by as much as a centimeter, depending on how full your bladder and rectum are. IGRT approach has a lot of flexibility, because the radiation oncologist uses CT scan images to point the exact location of the prostate each day.

Perirectal sparing with placement biomaterials between the posterior prostate and the anterior rectum has shown promise in reducing the radiation dose received by the rectal wall when used in the setting of conventional fractionated radiotherapy [7, 8]. Perirectal sparing biomaterials may promote not only sparing of the rectum wall but also result in decreased dose to other organs at risk including the penile bulb and bladder (**Figure 2**).

Linear accelerators equipped with kilovoltage (kV) cone-beam computed tomography (CBCT) allow for soft tissue registration immediately before treatment over the past decade [9]. Image guidance was either by implanted fiducials and daily kilovoltage imaging or with the use of cone-beam computed tomography (CBCT). IGRT is an excellent method for dose-escalated external beam radiotherapy in the treatment of localized prostate cancer in regard to GU and GI toxicity (**Figure 3**).

It is well documented that the prostate bed is highly susceptible to inter-fraction motion leading to larger treatment planning margins to account for daily treatment setup uncertainties when matching bony anatomy. Organ motion can be a significant barrier to delivering accurate external beam radiotherapy to the prostate. The use of fiducial markers in the prostate bed has significantly improved the accuracy of the treatment delivery.

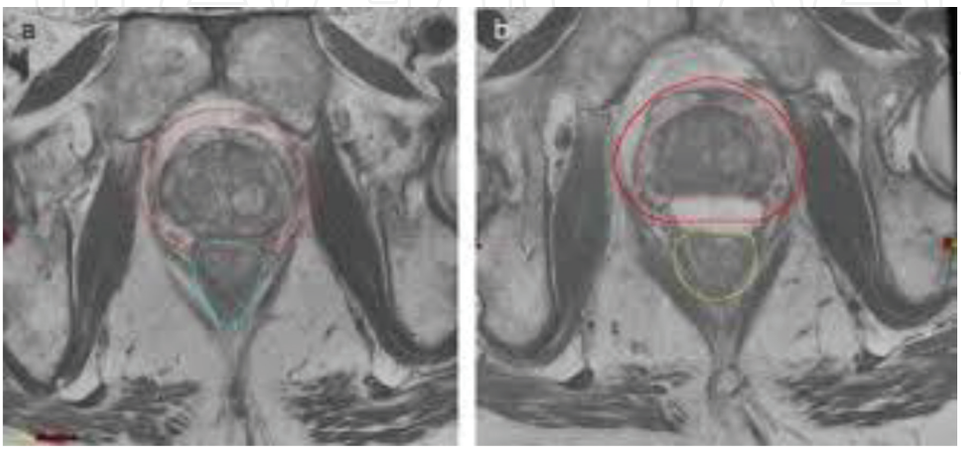

Figure 2. MR images of perirectal sparing with biomaterials and without it.

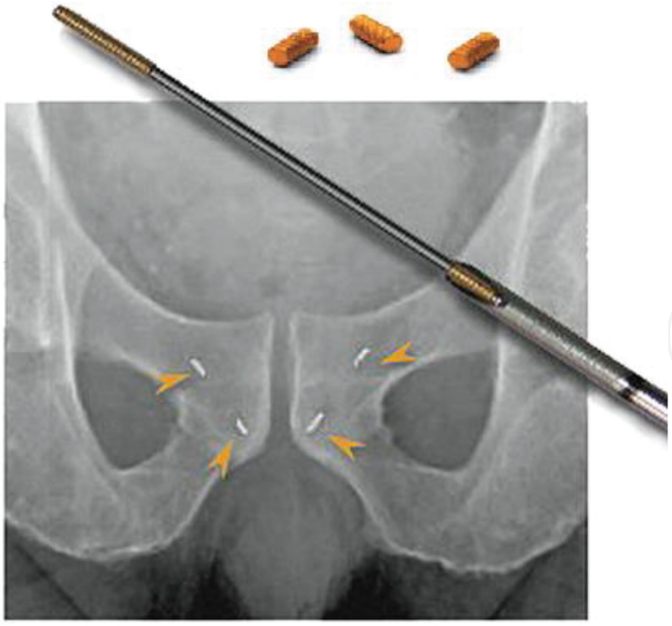

Figure 3. Fiducial markers image.

With CBCT scan-based correction strategies, one should be able to overcome the limitations of marker-based strategies. Smitsmans et al. [10] developed an automatic, rigid, three-dimensional (3D) gray-value registration (3D-GR) method for fast prostate localization on CT scans. In a following study, they showed that the 3D-GR prostate localization also worked with CBCT scans and concluded that CBCT scans could be used for image-guided radiotherapy for prostate cancer [11]. Using the daily CBCT scans, we could compare today's images with yesterday's and tune the treatment accordingly. Many studies have been reported on image guidance strategies to correct for prostate motion with daily offline or online position verification of the prostate. Most of these reports used implanted fiducial markers in the prostate [12, 13]. Although fiducial marker-based correction strategies are already an important step forward, they have some shortcomings. The implantation of markers is an invasive procedure. Marker-based strategies correct for translations but tend to neglect rotations, which are known to be a large component of prostate motion [14]. Also, marker-based correction strategies do not take into account changes in position of the seminal vesicles or the effect of a changed anatomy on planning, especially relevant for IMRT.

The Calypso® (Varian Medical Systems, Palo Alto, USA) system uses radio-frequency waves that allow very accurate alignment of the prostate before each treatment session and at all times during treatment delivery. The Calypso® system improves the ability to target radiation only to tumor volume, avoiding unnecessary radiation to healthy tissues such as the bladder and rectum. The Calypso localization and tracking system works with three Beacon® transponders, wireless electromagnetic circuits about the size of a grain of rice, that are implanted in the prostate. It is shown in **Figure 4**. The Calypso® system works with the transponders to locate the tumor's position, guide the therapist to set up the treatment continuously through radiotherapy, and tailor treatment delivery to trigger the beam on and off to ensure the tumor is accurately aligned throughout the treatment [15]. In addition, the data demonstrate that treatment with VMAT permits the use of advanced prostate tracking (Calypso®), resulting in similar treatment times as standard seven-field

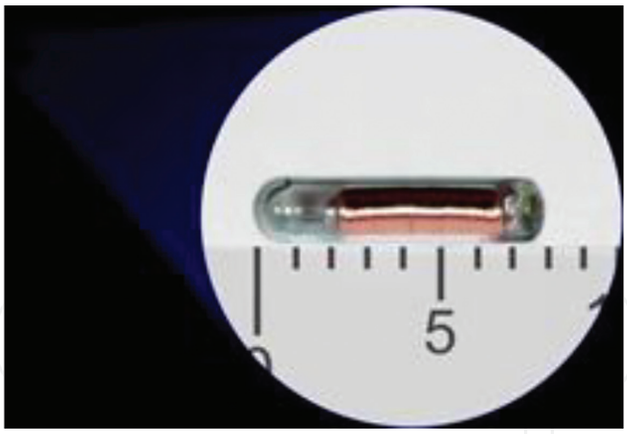

Figure 4. A Beacon® transponder.

dynamic multileaf collimator (DMLC) IMRT with conventional tracking [16]. Foster et al. [17] determined the differences between CBCT-Calypso® and kV imaging-Calypso® localizations are 0.31 ± 1.82, 0.00 ± 1.00, and − 028 ± 1.36 and 0.28 ± 4.12, −0.28 ± 3.22, and 0.16 ± 1.61 mm, respectively, in the AP, SI, and RL directions during 160 and 100 fractions each These results show good localization agreement between radiographic technique and electromagnetic transponder technique, indicating that each of the localization technique is suitable for prostate cancer.

The functionality of RayPilot® (Micropos Medical, Sweden) is similar to a GPS by means that a target is localized with given coordinates. The system communicates with an implanted transmitter that is located in the ROI to be treated. The transmitter sends signals to a sensor plate 30 times per second, and the position is presented in the software. The system consists of the RayPilot® receiving system which is placed on any existing treatment couch, the RayPilot transmitter that is placed in the ROI, and the RayPilot® software. Initially, the system is used in treatment of prostate cancer as IGRT system [18].

Noninvasive 4D transperineal ultrasound (4D-TPUS) has been introduced in tracking intrafractional prostate motion in radiotherapy. Compared to other tracking methods, the ultrasound has its own advantage in precise identification of the soft tissue without invasive procedure or extra radiation dose. In addition, system supplies contouring tool for prostate and OAR volume while doing CT/ultrasound image fusion in the same patient position. Clarity® (Elekta AB, Stockholm, Sweden) 4D monitoring during prostate treatment offers live imaging of the target and surrounding anatomy. The target position is automatically calculated and compared to physician action thresholds to enable intrafraction motion management (**Figure 5**).

Ultrasound provides real-time position data for the prostate that was used to gate the treatment. Ultrasound motion data provides margin guidelines for clinics without ultrasound that treat prostate SBRT with a rectal balloon, based on their expected treatment length and acceptable probability of prostate excursion beyond margins. Qi et al. [19] determined the median (5–95% percentile) of 221 intrafraction prostate motions in the L−/R+, S+/I−, and A+/P− were 0.1 mm (−1.13 to 1.64 mm), −0.1 mm (−1.89 to 1.90 mm), and − 0.3 mm (−2.88 to 1.25 mm) by using 4D-TPUS. There were 70/221 (32%) fractions with deviation exceeding 2 mm in any direction, with an average duration of 26% of treatment time, while there were 19/221 (8.6%)

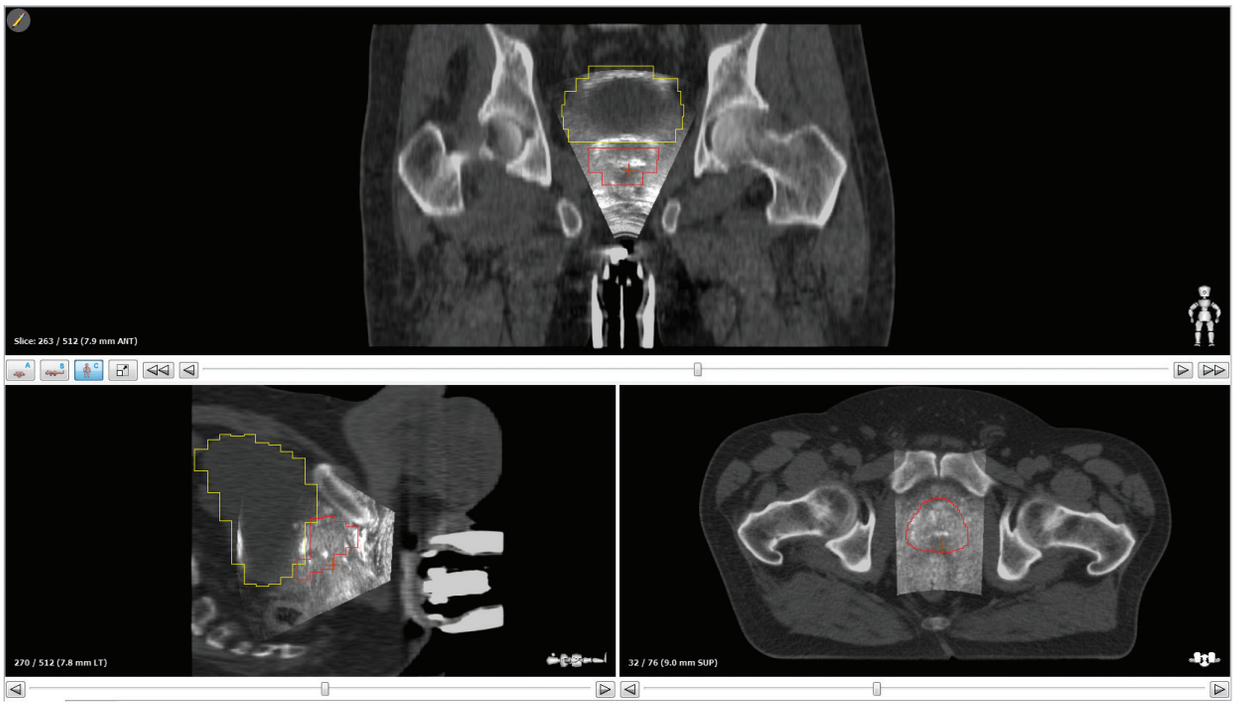

Figure 5. Image fusion between CT and ultrasound.

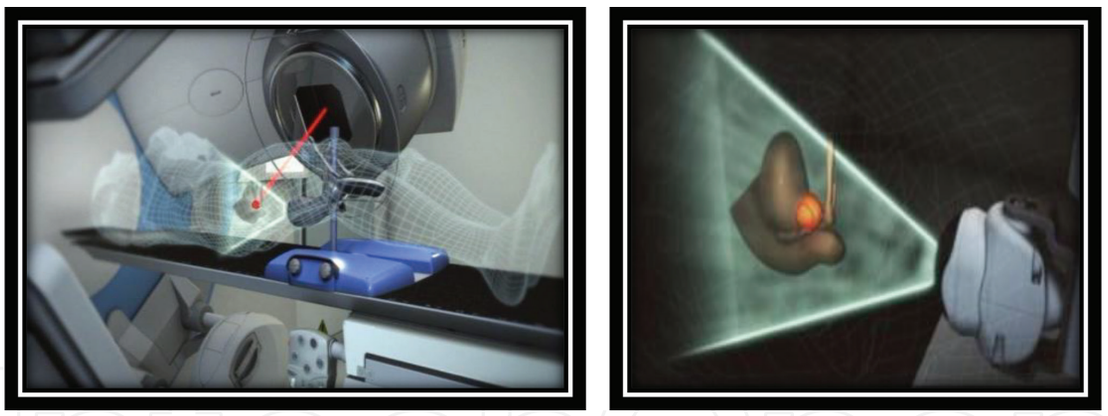

Figure 6. 4D transperineal ultrasound scanning.

fractions with deviation exceeding 3 mm in any direction with an average duration of 6.3% of treatment time. These data can help to understand the intrafraction motion of the prostate and may allow a reduction of treatment margin (**Figure 6**).

2.5. Hypofractionation radiotherapy technique

Many studies have shown a lower α/β value (1.4–3.1 Gy) for prostate cancer than most of other cancers. This indicates that prostate cancer would be more responsive to the size of fractional dose rather than the total dose. Due to this radiobiological feature, the hypothesis is that hypofractionation would yield non-inferior or even better local control than conventional fractionated radiotherapy without increasing the risk of treatment-related toxicities. A series

of equivalent hypofractionation regimens suitable for the IMRT simultaneous integrated boost (SIB) were obtained for high-risk prostate cancer. For example, the conventional treatment regimen of 42 × 1.8 Gy (EUD = 75.4 Gy) would be equivalent to a SIB regimen of 25 × 2.54 Gy. Compared to the conventional two-phase treatment, the proposed SIB technique offers potential advantages, including better sparing of critical structures, more efficient delivery, shorter treatment duration, and better biological effectiveness for high-risk prostate cancer treatment [20].

Hypofractionated image-guided radiotherapy with 15 fractions of 3.65 Gy/3 weeks is well tolerated with a low rate of acute and late grade ≥ 2 GI and GU toxicities. This schedule permits to obtain a high rate of survival and disease control with reduction of treatment time spent for treatment by patients [21]. Hypofractionated intensity-modulated radiotherapy of 45 Gy in nine consecutive fractions' regime for mainly low−/intermediate-risk prostate cancer patients is favorable with low rates of late toxicity [22]. Hypofractionated radiotherapy with IMRT-IGRT as primary treatment for prostate cancer allows reduction in overall treatment time without compromising outcomes. This Hypo-IMRT with IGRT schedule for prostate radiotherapy reduces treatment length by 2 weeks as compared to the other treatment regimens commonly used.

Compared with conventional radiotherapy, hypofractionated radiotherapy has achieved similar clinical outcomes in patients with intermediate-to-high-risk localized PCa. Although hypofractionated radiotherapy has an increased incidence rate of acute gastrointestinal adverse events, the late gastrointestinal and genitourinary adverse events were similar in two groups and could be tolerable for the patients.

2.6. Stereotactic body radiotherapy (SBRT) technique

Stereotactic body radiotherapy (SBRT) is an established treatment technique for prostate cancer. High dose per fraction radiotherapy has theoretical advantages when treating "late responding tissue." SBRT for high-risk prostate cancer (PCa) remains investigational not only due to concerns for potential toxicity when the treatment volumes extend beyond the prostate gland itself. Specifically, some investigators have reported high rates of toxicity when targeting elective pelvic nodal irradiation volumes with SBRT techniques, but technical considerations may have influenced those results. SBRT regimes can be safely used to treat patients with high-risk PCa in a total of 5 treatment days. The addition of pelvic nodal radiation did not significantly increase acute or late genitourinary or gastrointestinal toxicity on either physician- or patient-reported scales [23].

Dose escalation beyond currently standard SBRT regimens may further improve outcomes, particularly for bulkier tumors, but could be limited by organ dose constraints. However, selective dose escalation to identified regions of high tumor burden may offer a safer approach than uniform dose escalation, thereby maximizing therapeutic ratio. Therefore, this ongoing prospective study seeks to test the planning and delivery feasibilities and the tolerability of treating patients with a modest dose escalation to the entire prostate and a SIB to magnetic resonance (MR)-identified lesions (**Figure 7**).

Chapet et al. [24] compared acute toxicities of moderate hypofractionation versus stereotactic radiation for prostate cancer. They determined that hypofractionation and SBRT are well tolerated in only two grade 3 acute GU toxicities and only one grade 3 GI toxicity. There is no

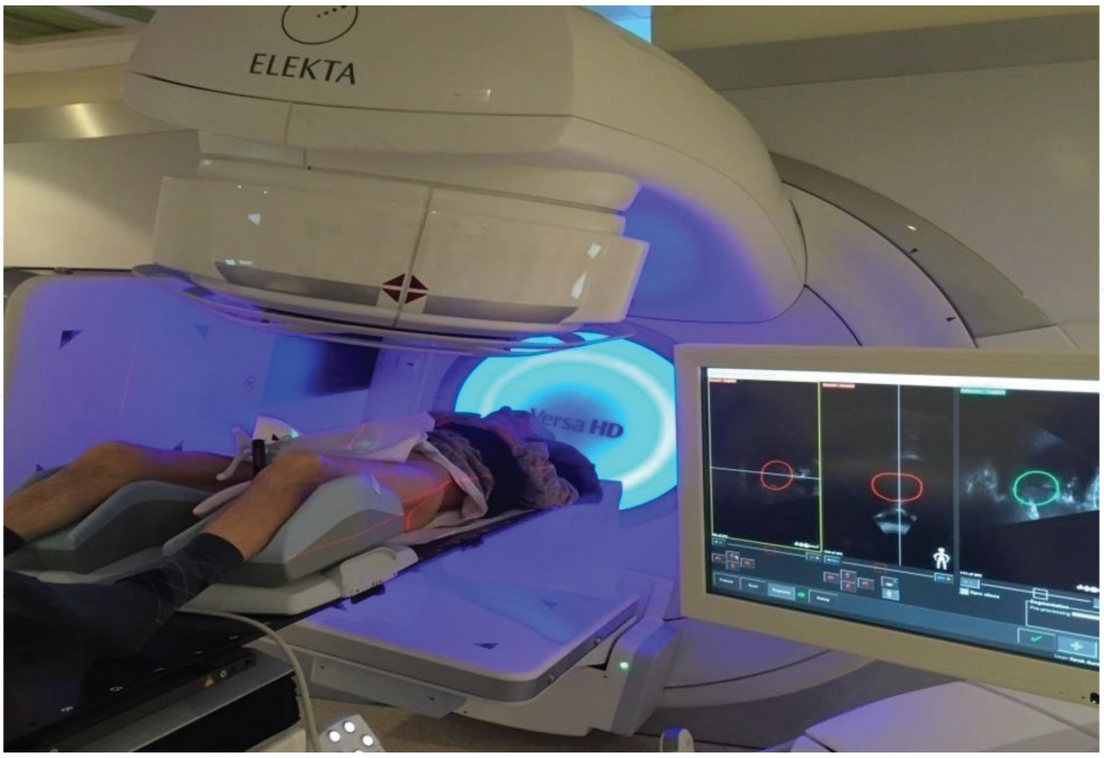

Figure 7. Prostate SBRT treatment by using 4D TPUS Clarity® IGRT system and versa HD® linear accelerator.

difference in grade ≥ 2 acute toxicities, the acute profile of tolerance appears to be the same between hypofractionation and SBRT for urinary toxicities, and acute GI toxicities seem to be well controlled by the spacer whatever fractionation is used.

SBRT for prostate cancer has become increasingly popular, but the use of hypofractionation necessitates special consideration of the normal tissue tolerances of organs such as the urethra, bladder, and rectum. Tracking prostatic motion in real time provides more precise treatment by allowing a repositioning of the treatment couch if the fiducials move outside a threshold margin. Although soft tissue anatomy is not readily visualized in real time during treatment, fiducial marker position is used as a surrogate for target/organ-at-risk geometry. Because of the observed random distribution of motion, we hypothesize that CBCT's performed before and after treatment may miss intrafraction movements that exceed the threshold margin. Due to intrafractional movement, positioning the patient exclusively based on the pretreatment CBCT scans is insufficient to ensure complete target coverage. Intrafractional on-demand imaging is required to ensure adequate coverage to the PTV.

Robotic SBRT of soft tissue lesions using Cyberknife® (Accuray, Sunnyvale, USA) requires implantation of fiducial markers for target tracking by the stereoscopic KV X-ray imaging system. The spatial distribution of the fiducials must allow accurate calculation of 3D transformation that describes the position of the prostate within the reference frame of the planning CT scan. Poor fiducial placement limits accurate tracking. Creating fiducial implantation protocol could improve ability to accurately track prostate motion during treatment. In order to take into account intrafraction rotation, a minimal spacing of 1.8 cm must be achieved between

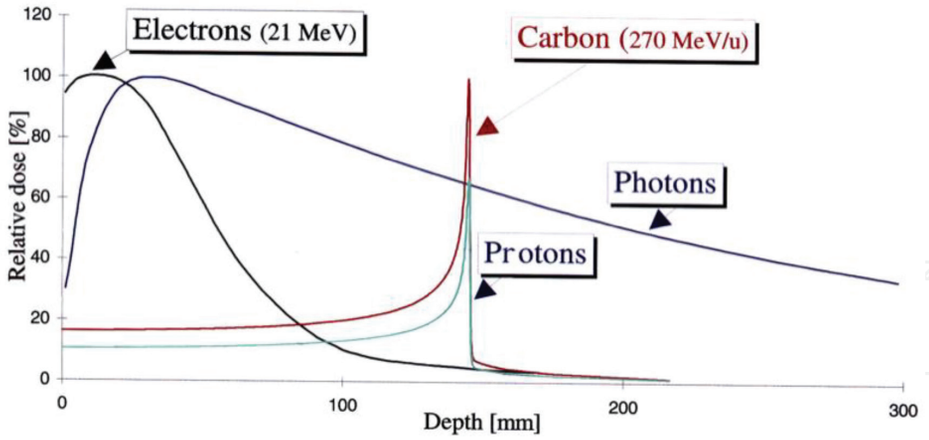

Figure 8. Depth dose curves of electron, photon, proton, and carbon beams.

implanted markers. This is frequently accomplished with double-loaded needles with spacers present or rigidly attached to the markers.

Advanced IGRT methods such as ultrasound, EMF, etc. with perirectal sparing biomaterials and/or fiducial markers can supply significantly advantage for accurate hypofractionation and SBRT treatment of prostate cancer.

Protons have completely different dose distribution properties and have the potential to avoid most of the extra-target radiation that is inherent to photons. Unlike a photon, a proton is a heavy particle (roughly 1800 times the mass of an electron) with an elementary charge, which confers certain dosimetric advantages. Heavy particles, as opposed to photons, will stop within a target. This unique property allows protons to be targeted so that they have their most damaging effects in the tumor itself, with less radiation delivered in front of the target, and no dose delivered beyond it. This peak of energy delivery is commonly referred to as the Bragg peak. It is shown in **Figure 8**. The Bragg peak is very narrow and must be spread out using multiple proton energies to ensure that the peak encompasses the entire target.

Proton beam therapy for prostate cancer has become a source of controversy in the urologic community, and the rapid dissemination and marketing of this technology have led to many patients inquiring about this therapy. Several groups [25–30] have investigated the dosimetric quality of proton therapy for prostate cancer. Rana et al. [31] determined the average difference in the PTV doses between the VMAT and lateral two-field proton plans was within ±1%. On average, the proton plans produced a lower mean dose to the rectum (18.2 Gy (relative biological effectiveness [RBE]) vs. 40.0 Gy) and bladder (15.8 Gy (RBE) vs. 30.1 Gy), whereas the mean dose to the femoral heads was lower in the VMAT plans (28.3 Gy (RBE) vs. 19.3 Gy).

Magnetic resonance images (MRI) demonstrate superior soft tissue contrast such as the prostate, rectum, bladder, etc. than CT scans. MR based-linac offers a clinically proven on-table MRI-guided online adaptive, automated and integrated treatment planning system that uses a linac to deliver modulated radiotherapy. Magnetic resonance radiotherapy (MR/RT) system is capable of delivering precisely targeted radiation doses while simultaneously capturing magnetic resonance (MR) images. We expect significantly decreased target margin and increased target dosage by using online adaptive MRI-based linac in the future (**Figure 9**).

Figure 9. MR-based linac Elekta Unity® and ViewRay® MRIdian.

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